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Health and Environmental Effects Profile for Phosphorothioic Acid, Trimethyl Esters

(U.S.) Environmental Protection Agency
Cincinnati, OH

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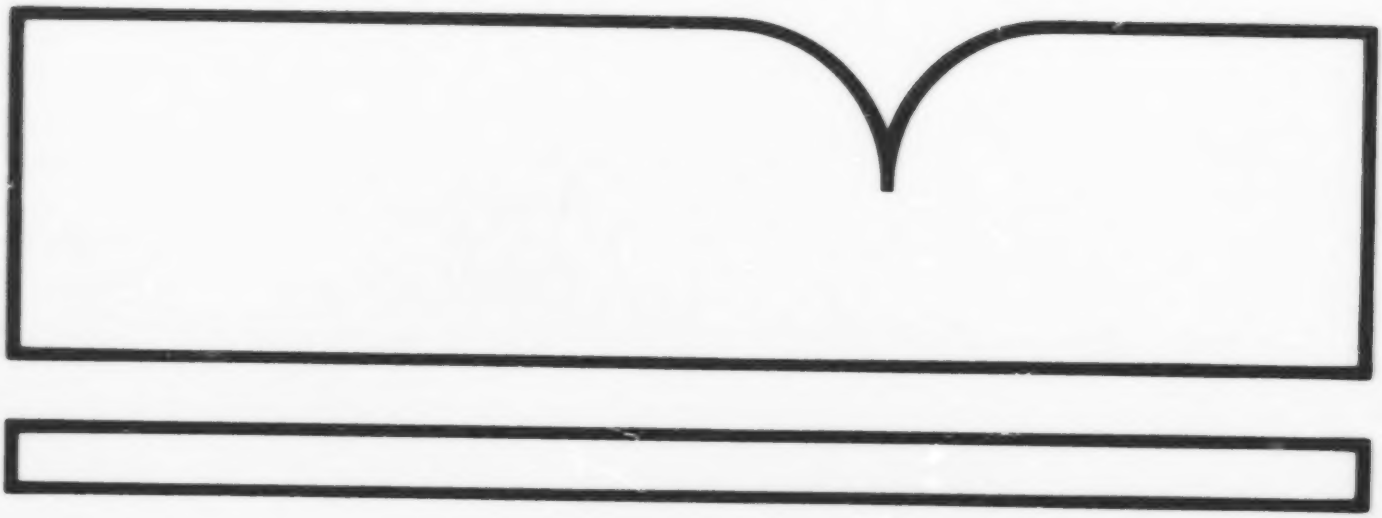

U.S. Department of Commerce
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January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR PHOSPHOROTHIOIC ACID, TRIMETHYL ESTERS

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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16. ABSTRACT

The Health and Environmental Effects Profile for Phosphorothioic Acid, trimethyl esters was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for Phosphorothioic Acid, trimethyl esters.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
i.p.	Intraperitoneal
i.v.	Intravenous
LD_{50}	Lethal dose to 50% of recipients
MFO	Mixed function oxidase

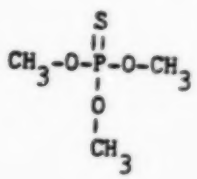
1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Phosphorothioic acid, 0,0,0-trimethyl ester is also known as methyl phosphorothioate, trimethylthiophosphate, 0,0,0-trimethylphosphorothioate and 0,0,0-trimethylthiophosphate.

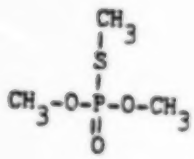
Phosphorothioic acid, 0,0,S-trimethyl ester is also known as dimethylthiomethyl phosphate, methylphosphorothioate and 0,0,S-trimethylphosphorothioate (NIOSH, 1983).

The structures and Chemical Abstracts Service (CAS) numbers of the compounds are given below:



Phosphorothioic acid, 0,0,0-trimethyl ester

CAS No. 152-18-1
Molecular formula: $C_3H_9O_3PS$
Molecular weight: 156.15



Phosphorothioic acid, 0,0,S-trimethyl ester

CAS No. 152-20-5
Molecular formula: $C_3H_9O_3PS$
Molecular weight: 156.15

These trimethyl esters of phosphorothioic acid will be referred to as the 0,0,0-ester and the 0,0,S-ester throughout this profile.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

The 0,0,0-ester is a colorless liquid with a boiling point of 78°C at 12 mmHg (Hawley, 1981). No other physical properties for this chemical were located in the available literature.

Pertinent data regarding the physical and chemical properties of the 0,0,S-ester were not located in the available literature.

1.3. PRODUCTION DATA

Pertinent data regarding the production of the O,O,O-ester and the O,O,S-ester were not located in the available literature, nor were these chemicals listed in the 1977 TSCA Inventory File (U.S. EPA, 1983).

Toxicologic studies indicate that these chemicals are among the impurities in technical organophosphorus insecticides such as malathion and fenthion (Toia et al., 1980; Aldridge et al., 1979). Pellegrini and Santi (1972) estimated that the O,O,S-ester comprised 0.1% of technical malathion (92.2% active ingredient).

1.4. USE DATA

The O,O,O-ester is used in the extraction of mineral salts from alkyl acid phosphate solvent solutions and as a plasticizer (Hawley, 1981).

Pertinent data regarding uses of the O,O,S-ester and other uses of the O,O,O-ester were not located in the available literature.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Very little information on the environmental fate of the 0,0,0-ester and the 0,0,S-ester was located. The SRC's Environmental Fate Data Base contained only one citation, which reported that the relationship of the second order alkaline hydrolysis rate constant (4.8×10^{-5} M^{-1} sec^{-1} at 27°C) and the pK_a of the conjugate methyl leaving group (15.5) for the 0,0,0-ester indicated that hydrolysis will be slow under most environmental conditions (Wolfe, 1980).

In an abstract from a Chinese study (Kuan et al., 1979), it was reported that at pH 11.8 the half-life for hydrolysis of the 0,0,0-ester was 10-200 hours at 30-60°C. At pH 7.2, the half-life was 1300 hours at 40°C.

Pertinent data regarding the environmental fate of the 0,0,S-ester or further data on the fate of the 0,0,0-ester were not located in the available literature.

3. EXPOSURE

No monitoring data on the 0,0,0-ester and the 0,0,S-ester were encountered in STORET or any other source.

4. PHARMACOKINETICS

4.1. ABSORPTION

Imamura et al. (1983a) administered [$^{14}CH_3S$]-labeled-0,0,S-ester (20 mg/kg bw) by gavage to male Sprague-Dawley rats and found a maximum blood level of parent compound of 50 nmole/g within 20-120 minutes. Information on absorption was also obtained from a study designed to elucidate the mechanism of delayed toxicity of the 0,0,S-ester and the inhibitive effect of the 0,0,0-ester on this toxicity (Hammond et al., 1982a). Following oral administration of [$^{14}CH_3O$]-labeled 0,0,S-ester (9.37x10^6 dpm/kg bw or 60 mg/kg bw in corn oil) to female Sprague-Dawley rats, a maximum blood level of ~450 dpm/100 mg blood was achieved within 10-30 minutes. When the 0,0,0-ester was coadministered (3 mg/kg bw), the maximum level was reduced to ~300 dpm/100 mg blood. Thus, the 0,0,S-ester was absorbed from the gastrointestinal tract of rats following oral administration (Imamura et al., 1983a; Hammond et al., 1982a), but the amount (not rate) of absorption was reduced by coadministration of the 0,0,0-ester (Hammond et al., 1982a).

4.2. DISTRIBUTION

In the previously described study, Hammond et al. (1982a) found that the blood level of radioactivity (maximum ~450 dpm/100 mg blood) in rats following oral treatment with [$^{14}CH_3O$]-0,0,S-ester remained elevated for 180 minutes, at which time the concentration had fallen only to ~400 dpm/100 mg blood. Imamura et al. (1983a) reported that in rats receiving 20 mg/kg of [$^{14}CH_3S$]-0,0,S-ester by gavage, the peak blood level (50 nmole/g) of radiolabel associated with the parent compound was reached in 20-120 minutes, and then declined with a half-life of 190 minutes. Radiolabel that was not associated with parent compound (i.e., a radioactive metabolite) was still detected in blood at a level of 10 nmole/g at 30 hours after dosing.

Hammond et al. (1982a) also studied the pattern of distribution of ^{14}C in rats following i.v. administration of 60 mg [$^{14}CH_3O$]-0,0,S-ester/kg bw without coadministration of the 0,0,0-ester (3 mg/kg). The blood concentration of radiolabel declined rapidly from 4500 to ~1100 dpm/100 mg blood within 30 minutes of injection of the 0,0,S-ester and remained at this level for 180 minutes of observation. The coadministration of the 0,0,0-ester did not alter this pattern. Radiolabel was detected 50-53 hours after i.v. injection of ^{14}C-0,0,S-ester in the kidneys, adrenals, lungs, liver, spleen, stomach, stomach contents, large intestine, large intestine contents, small intestine, small intestine contents, heart, whole brain and thymus. The highest concentrations were present in the liver, kidneys and adrenals. When the 0,0,0-ester was co-injected, only the concentration of radiolabel in the contents of the large intestine was decreased significantly ($p<0.002$), with appreciable decreases in the stomach and small intestines and their contents ($p<0.1$).

4.3. METABOLISM

Malik and Summer (1982) observed that incubation of rat hepatocytes ($3.3x10^6$ cell/mℓ) with 0.05 mℓ of 1 mM 0,0,S-ester in DMSO (DMSO had no effect on hepatocyte viability) resulted in ~20% depletion of glutathione without the formation of glutathione disulfide, indicating that glutathione was involved in the metabolism.

Imamura et al. (1983a,b,c) suggested that following oral treatment of rats with the 0,0,S-ester, a metabolite was formed in the lungs by the action of the mixed function oxidase (MFO) system, and was responsible for the delayed pulmonary toxicity of the 0,0,S-ester (see Section 5.6.). As previously discussed, there is evidence that, following the administration of [$^{14}CH_3S$]-0,0,S-ester by gavage to rats, a radioactive metabolite

persisted in the blood for 30 hours (Imamura et al., 1983a). The metabolite was not identified.

Pertinent data regarding the metabolism of the O,O,O-ester were not located in the available literature.

4.4. EXCRETION

Pertinent data regarding excretion of the O,O,O-ester and the O,O,S-ester were not located in the available literature. Elimination of the parent compound from blood and evidence for the persistence of a metabolite in blood (Imamura et al., 1983a) have been discussed in Sections 4.2. and 4.3.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of the O,O,O-ester and the O,O,S-ester were not located in the available literature and these chemicals are not scheduled for testing by the National Toxicology Program (NTP, 1983).

5.2. MUTAGENICITY

Pertinent data regarding the mutagenicity of the O,O,O-ester and the O,O,S-ester were not located in the available literature.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of the O,O,O-ester and the O,O,S-ester were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of the O,O,O-ester and the O,O,S-ester were not located in the available literature.

5.5. CHRONIC TOXICITY

Pertinent data regarding the effects of chronic exposure to the O,O,O-ester and the O,O,S-ester were not located in the available literature.

5.6. OTHER RELEVANT INFORMATION

The following LD_{50} values for the O,O,S-ester were listed by NIOSH (1983):

oral	rat	15 mg/kg
i.v.	rat	45 mg/kg
oral	mouse	134 mg/kg
i.v.	mouse	123 mg/kg

Goyer and Cheymol (1967) reported the LD_{50} in mice for i.p. injection of the O,O,S-ester to be 135 mg/kg bw (observation period not specified) and found a correlation between mouse LD_{50}s and anticholinesterase activity in guinea pig brain tissue and chicken serum.

The O,O,S-ester has been studied extensively for its effects after acute exposure and has been shown to have delayed toxicity. Mallipudi et al. (1979) reported that in rats the acute oral LD_{50} was 200 mg/kg when the observation period was 48 hours, but the LD_{50} was reduced to 15-20 mg/kg when holding period was extended to 25 days.

The major sign of toxicity in rats that received 15 or 30 mg O,O,S-ester/kg bw by gavage was weight loss. At higher doses (40-200 mg/kg bw by gavage), signs of toxicity included anorexia and weight loss, heavy diarrhea and urination, and bleeding of the mouth, nose and ears (Mallipudi et al., 1979; Umetsu et al., 1981). Additional observations in rats that received 20-200 mg/kg of the O,O,S-ester by gavage were narcosis and increased lung weight associated with histological lung damage (Verschoyle and Cabral, 1982; Aldridge et al., 1979; Imamura et al., 1983b); hemorrhagic lungs, liver, intestines and stomach (Umetsu et al., 1981); and liver necrosis, the severity of which was dose related at 30-200 mg/kg bw (Hammond et al., 1982b).

With respect to the lung damage observed in rats, Imamura et al. (1983b) have reported morphological changes in nonciliated Clara cells of the bronchiolar epithelium of rat lungs associated with an increased activity of lactate dehydrogenase in bronchopulmonary lavage fluid 3 days following treatment by gavage with 20 mg O,O,S-ester/kg bw. In addition, rats treated with doses of 20 and 40 mg/kg bw had increased activities of carboxylesterases in pulmonary alveolar macrophages that were maximal 1 day after treatment (Imamura et al., 1983c). It was suggested that the lung damage was a result of the action of a toxic metabolite of the O,O,S-ester formed following induction by the O,O,S-ester of MFOs of the Clara cells and macrophages.

The 0,0,S-ester has been found to potentiate the toxicity of malathion, reducing the oral LD_{50} of malathion in the rat by ~1/2 when present at very low levels (0.18% of malathion) (Pellegrini and Santi, 1972).

Single gavage doses of 15, 40 or 60 mg 0,0,S-ester/kg bw caused a prolonged (up to 14 days) inhibition of serum cholinesterase and carboxylesterase activities in rats. Coadministration of the 0,0,0-ester shortened the period of inhibition (Umetsu et al., 1981).

The 0,0,0-ester appears to be less toxic than is the 0,0,S-ester. LD_{50} values for the 0,0,0-ester in mice were reported as 1070 mg/kg bw when administered intraperitoneally (observation period not specified) (Goyer and Cheymol, 1967) and 1150 mg/kg bw when given orally with a 48-hour observation period (Toia et al., 1980). As with the 0,0,S-ester, signs of toxicity in mice included reduced respiratory rates and prostration. In rabbits given 20 mg/kg bw i.v., symptoms were sialorrhea, lacrimation, myosis, muscular fasciculation, defecation and conbulsion (Goyer and Cheymol, 1967). Three i.v. injections of the 0,0,0-ester (5-20 mg/kg bw) administered to rabbits during a 3-hour period resulted in a dose-related decrease in acetylcholinesterase activity of red blood cells. A relationship between symptom intensity and enzymic inhibition following acute intoxication was also reported (Goyer and Cheymol, 1967). The 0,0,0-ester weakly potentiated the toxicity of malathion (Toia et al., 1980), whereas, pretreatment, coadministration or post-treatment (up to 4 hours) orally with the 0,0,0-ester at doses of 1-5% of the 0,0,S-ester protected rats against the toxicity of the latter isomer (Hammond et al., 1982a; Umetsu et al., 1979) and, as previously discussed, shortened the duration of cholinesterase inhibition by the 0,0,S-ester (Umetsu et al., 1981).

6. AQUATIC TOXICITY

Pertinent data regarding the toxic effects of the trimethyl esters of phosphorothioic acid on aquatic organisms were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent data regarding existing guidelines for the O,O,O-ester and the O,O,S-ester were not located in the available literature.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of the trimethyl esters of phosphorothioic acid were not located in the available literature.

8. RISK ASSESSMENT

The lack of pertinent data regarding either the carcinogenic potential of the 0,0,0-ester and the 0,0,S-ester or the effects of chronic exposure to these chemicals precludes the assessment of carcinogenic risk or the derivation of an ADI value. In acute experiments, the 0,0,S-ester is more toxic than is the 0,0,0-ester (see Section 5.6.). The 0,0,S-ester has significant delayed acute toxicity, and produces prolonged inhibition of serum cholinesterase and carboxylesterase activities. Pulmonary and hepatic damage have been observed in rats administered acutely toxic doses of the 0,0,S-ester by gavage (Verschoyle and Cabral, 1982; Aldridge et al., 1979; Imamura et al., 1983b; Hammond et al., 1982b).

Both trimethyl esters of phosphorothioic acid have been detected as impurities in technical organophosphorous insecticides (including malathion). The 0,0,S-ester potentiated the acute toxicity of purified malathion in rats and is thought to be at least partially responsible for the finding that animals can tolerate higher doses of purified malathion than they can of technical (i.e., contaminated) malathion (Pellegrini and Santi, 1972).

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
TSCAPP
AQUIRE
EPCASR
Chemical Industry Notes

These searches were conducted in May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. 486 p.

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